REMARKS

In the June 20, 2000 Office Action, claims 1-3 and 5-7 were rejected, and claim 4 and 8 were objected to. Following entry of the above amendment, claims 1-9 will be pending in the subject application. Reconsideration is respectfully requested in light of the following remarks.

In the above amendments, applicants have added new claim 9, which recites that the dyskinesia being treated by an AMPA receptor antagonist is a dyskinesia "caused or exacerbated by" dopamine agonist therapy. Support for this amendment can be found in the originally-filed specification. For example, page 3 of the subject specification states that the phrase "dyskinesia associated with dopamine agonist therapy" used in the application means any dyskinsia which accompanies, or follows in the course of, dopamine agonist therapy, or which is caused by, related to, or exacerbated by dopamine agonist therapy (emphasis added herein). Since support for the above amendment can be found in the originally-filed application, applicants maintain that the amendments herein do not raise an issue of new matter and respectfully request that the above amendment be entered.

The Examiner indicated that claims 4 and 8 are directed to allowable subject matter, but are objected to as being dependent from rejected claims.

The Examiner rejected claim 1-3 and 5-7 under 35 USC 103(a) as allegedly obvious over Arnold, et al., U.S. Patent 5,670,516. The Examiner asserted that Arnold et al. teaches a method of treating neurological disorders by administering a compound that blocks or antagonizes AMPA receptors. According to the Examiner, the invention recited in the claims of the present application is directed to a more specific neurological disorder, namely dyskinesia associated with dopamine agonist therapy. The Examiner stated that a person of ordinary skill in the art would have been motivated to treat dyskinesia [associated with dopamine agonist therapy] using an AMPA receptor antagonist in view of Arnold et al. because Arnold et al. supposedly teach that dyskinesia is among the neurological disorders responsive to AMPA antagonists (citing claims 24 and 29 of Arnold et al.).

Applicants respectfully traverse. Arnold et al. refers to a list of "neurological disorders", including "tardive dyskinesias" in Column 3 that can be treated by the

compounds of formula I therein indicated to be AMPA receptor antagonists (see Column 3, lines 30-46). It appears clear from such context that said tardive dyskinesias referred to in Arnold et al. are dyskinesias that are symptomatic of or caused by neurological disorders, for example Parkinson's disease, which is also recited in the list in Arnold et al. Although the Examiner pointed out that "mechanisms of action as to how a particular condition, disease, etc. works are not afforded patentable weight under the current U.S. law", this precept is not applicable to the instant facts. Here, applicants are urging that the *indication* referred to in Arnold is qualitatively different from the *indication* recited in applicants' claims. Arnold et al. refers to tardive dyskinesia which is caused by neurological disorders such as Parkinson's disease, whereas the claims relate to dyskinesia caused by dopamine agonist therapy. The aforementioned rule which the Examiner has set forth applies to facts wherein the indication is the same, albeit caused by two different mechanisms. It is clear that dyskinesia caused by the mechanisms underlying Parkinson's disease do not also have dopamine agonist therapy as a contributing factor, since dopamine agonist therapy actually *reduces* such dyskinesias, as described in references such as Klockgether et al. and Stella et al, discussed *infra*. In view of the above discussion, applicants respectfully request that the Examiner reconsider and withdraw the rejection of the claims of the subject application over Arnold et al.

The Examiner also rejected claims 1-3 and 5-7 under 35 USC 103(a) as allegedly obvious over Klockgether, et al. The Examiner stated that Klockgether et al. teaches that blocking AMPA receptors by administering AMPA receptor antagonists may provide a new strategy for treating Parkinson's disease. The Examiner argued that a person of ordinary skill in the art would have been motivated to develop a method for treating dyskinesia associated with L-dopa therapy based on Klockgether et al. because Klockgether et al. supposedly suggests treating Parkinson's disease patients who are on L-dopa therapy and that AMPA antagonists can potentiate the actions of l-dopa and reduce tremor associated therewith. The Examiner also argued that Klockgether et al. suggests treating dyskinesia associated with l-dopa therapy since Parkinson's disease symptoms include tremors which results in dyskinesia. The Examiner characterized Klockgether et al. as teaching that co-administration of an

AMPA antagonist and L-dopa was conducted to reduce symptoms typically associated with Parkinson's disease, including tremors and dyskinesia; and that, in such co-administration, the AMPA receptor antagonist potentiates or makes l-dopa more effective in the treatment of Parkinson's disease symptoms because "it reduces or eliminates side effects associated with the administration of either antagonist or l-dopa drug", citing page 720, first column, lines 8-10.

Applicants respectfully traverse. First, Klockgether et al. does not state at page 720, first column, lines 8-10, that NBQX (the AMPA receptor antagonist) reduces and/or eliminates side effects associated with the administration of l-dopa. The reference merely states at the cited portion, "no NBQX-related side effects (dyskinesias, vomiting, or apparent psychological disturbance) were seen in either monkey". Thus, all that is stated is that the AMPA receptor antagonist, NBQX, did not present any side effects. Nothing here is mentioned or implicated about reducing or eliminating l-dopa side effects. Granted, one of the monkeys to which the cited statement refers was a monkey with experimentally-induced Parkinson's disease which had been administered NBQX in combination with l-dopa. However, the l-dopa was administered at a dose that had alone produced only marginal improvement [in reducing parkinsonian symptoms] (see page 719, second column, the last three lines, of Klockgether et al.). There is no mention in Klockgether et al. that this monkey ever exhibited side effects due to the l-dopa administration. In fact, there is no mention that this monkey exhibited any side effects. All that is stated in Klockgether et al. is that this monkey "had severe parkinsonian rigidity in the left upper extremity" caused by the experimentally-induced Parkinson's disease (not either NBQX or l-dopa) (page 719, second column, the last paragraph, which continues on page 720).

Thus, at most, Klockgether et al. suggests that an AMPA receptor antagonist, NBQX, can be combined with dopamine agonist therapy to treat the symptoms of Parkinson's disease. It does not suggest that an AMPA receptor antagonist could be used for treatment of the effects of dopamine agonist therapy, such as dyskinesias associated with dopamine agonist therapy. Applicants furthermore maintain that Klockgether et al. suggests that use of an AMPA receptor antagonist might actually

result in dyskinesia such as those observed in chronic dopamine replacement therapy, e.g. dystonias and choreic dyskinesias (see the "Background" section of the subject application). Klockgether et al. also suggests that use of an AMPA receptor antagonist might actually aggravate such dyskinesias brought about by l-dopa therapy. It is noted that Klockgether et al. states that "[t]he principal findings of this research are that the selective AMPA receptor antagonist NBQX has potent antiparkinsonian effects in monoamine-depleted rats and MPTP-treated monkeys and that it potentiates the actions of L-dopa". Since NBQX is thus indicated in Klockgether et al. to have effects such as those produced by L-dopa, e.g. reduction in severe rigidity that is symptomatic of Parkinson's disease, it would seem to follow that NBQX might be expected to have the same side effects, e.g. choreic dyskinisias and dystonias, brought about by L-dopa therapy. True, Klockgether et al. further states, "NBQX did not produce apparent side effects *at the doses tested*" (emphasis added). However, applicants do not see how this statement provides insight or implication as to what effect NBQX would have at other doses or when chronically administered.

The Examiner noted that the instant specification at page 3 defines "dyskinesia associated with dopamine agonist therapy" as "any dyskinesia which accompanies, or follows in the course of, dopamine agonist therapy, or which is caused by, related to, or exacerbated by dopamine agonist therapy". However, Klockgether et al. does not describe administering a combination of l-dopa and NBQX to any animal afflicted with dyskinesia, let alone alleviation of dyskinesia in an animal which had been administered a combination of NBQX and l-dopa. The monkey, discussed above, to which a combination of l-dopa and NBQX was administered was described as exhibiting "rigidity".

Moreover, it is clear that the rigidity observed in the monkey in Klockgether et al. was not due to dopamine agonist therapy, but rather was due to the experimentally-inflicted Parkinson's disease; the monkey exhibited the rigidity before l-dopa was administered. Moreover, new claim 9, is directed to "a method of treating dyskinesia caused or exacerbated by dopamine agonist therapy". This claim is added to indicate what is being treated is dyskinesia caused by the dopamine agonist therapy. Applicants note, however, that the claim 9 still intends to cover administering an

AMPA receptor antagonist to a mammal while the animal is being treated with dopamine agonist therapy, as well as after the mammal has been treated with dopamine agonist therapy. Finally, applicants point out that the example (Example 1) in the specification of the subject application clearly demonstrates an AMPA receptor antagonist reducing dyskinesias induced in a monkey by dopamine agonist administration (L-dopa and PHNO). The situation described in the Example is unlike the monkey experiment discussed in Klockgether et al. in that in the latter, as discussed above, the rigidity was caused by a parkinsonian state in the monkey, whereas, in the former, the dyskinesias were caused by dopamine agonist administration.

The Examiner noted that Klockgether et al. states on page 723 that "[s]elective AMPA receptor antagonists have recently been reported to prevent neurotoxicity of L-dopa in an in vitro test system, and that they may therefore prevent some long term adverse effects of L-dopa treatment". This statement mentions neither "treatment" nor "dyskinesia associated with L-dopa therapy". It therefore does not render obvious use of an AMPA receptor antagonist to treat dyskinesia associated with dopamine agonist therapy, as claimed herein.

Accordingly, in light of the above, applicants maintain that claims 1-9 are not obvious from Klockgether et al.

The Examiner also rejected claims 1-3 and 5-7 under 35 USC 103(a) as allegedly obvious over Stella, et al. in view of Klockgether, et al., supra. The Examiner stated that Stella, et al. teaches administering glutamate antagonists to treat dyskinesias associated with l-dopa therapy in Parkinson's disease. The Examiner further stated that claims 1-3 and 5-7 differ because they recite administration of an AMPA receptor antagonist "as the glutamate antagonist". According to the Examiner, it would have been obvious to one of ordinary skill in the art to use AMPA antagonists as a glutamate antagonist, rather than "the NMDA antagonist". The Examiner asserted that one would have been motivated to make the substitution because Klockgether, et al. teach that both AMPA antagonists and NMDA antagonists are glutamate receptor antagonists, citing page 1, column 2, of Klockgether, et al. The

Examiner further alleged that applicants argued the Stella et al. and Klockgether et al. references separately and attacked the references individually.

Applicants respectfully traverse. Column 2 on page 1 of Klockgether et al. does not state that an AMPA receptor antagonist is a glutamate antagonist. Regardless, the discussion in Stella et al. regarding dyskinesia produced by levodopa/benserazide therapy is restricted to NMDA receptor blockade. Applicants noted in their last response that the statements in Klockgether et al. do not compensate for this deficiency, i.e. the limitation to NMDA receptor blockade, in Stella et al. because Klockgether et al. does not suggest that an NMDA receptor antagonist can be replaced with an AMPA receptor antagonist with the expectation of producing the same effect. This is not arguing the references separately. In that regard, column 2 of page 1 of Klockgether et al., if anything, suggests differences between AMPA antagonism and NMDA antagonism. More particularly, Klockgether et al. states at column 2 of page 1 that l-glutamate antagonists acting at the NMDA receptor have thus far been ineffective as anti-parkinson agents when administered systemically to primates. Klockgether at al. further states that since AMPA receptors are enriched in the subthalamic nucleus in comparison to NMDA receptors, AMPA antagonists may be effective in reducing activity of neurons in the STN. Accordingly, applicants maintain that it is not obvious from Stella et al. in view of Klockgether et al. to treat dyskinesia associated with dopamine agonist therapy using an AMPA receptor antagonist.

In conclusion, applicants maintain that claims 1-9 are directed to an unobvious inventions and that claims 1-9 are in condition for allowance. Applicants respectfully request the earliest possible notification of allowable subject matter.

If a telephone interview would assist in the prosecution of the subject application, the Examiner is invited to telephone applicants' undersigned attorney at the telephone number provided.

No fee is believed necessary in connection with filing this Amendment. However, if any fee is determined necessary in connection with filing this Amendment, authorization is hereby given to charge such fee to Deposit Account No.16-1445.

Respectfully submitted,

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